Advances in Inflammatory Bowel Disease

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Loftus Disclosures (last 12 months)

• Research support
  • AbbVie
  • UCB
  • Genentech
  • Janssen
  • Amgen
  • Pfizer
  • Takeda
  • Robarts Clinical Trials
  • Gilead
  • Receptos
  • Celgene
  • Medimmune
  • Seres Therapeutics

• Consultant
  • AbbVie
  • UCB
  • Janssen
  • Takeda
  • Mesoblast
  • Eli Lilly
  • Amgen
  • Bristol-Myers Squibb
Overview

• Existing treatment paradigms

• Evolving paradigms
  • Risk stratification
  • Treating earlier in disease course
  • Measuring objective inflammation to base treatment
  • Objective treatment endpoints
  • Therapeutic drug monitoring

• New therapies
Trends in Age- and Sex-Adjusted Incidence Rate of Crohn’s Disease (CD) and Ulcerative Colitis (UC): Olmsted County, Minnesota, 1970-2011

Shivashankar R et al, Am J Gastroenterol Suppl 2014
Changing Geographic Distribution of IBD
Pathogenesis of IBD

- Luminal antigens
- Genetic susceptibility
- Environmental triggers
- IBD

CP1169260 - 9
Main Susceptibility Genes for Crohn’s Disease

Extraintestinal manifestations
- e.g., psoriasis: IL23R, IL12B, PTPN22

Disease behaviour
- e.g., stenosis: NOD2, JAK2

Disease localization
- e.g., ileal involvement: NOD2

Predicting the disease phenotype
- Genotyping

Adaptive immunity
- Th17/Treg function
  - IL23R* 
  - IL12B* 
  - STAT3 
  - JAK2* 
  - TYK2 
  - CCR6 
  - IL2/IL21 
  - RORC 
  - ICOSLG* 
  - IL27 
  - VDR 
  - IL6ST 
  - OSM 
  - CD6 
  - PTPN22 
  - FASLG 
  - TACAP 
  - TNFSF15* 
  - TNFRSF9 
  - TNFRSF18 
  - TNFRSF6B 
  - NFKB1 
  - CD226 
  - IL10 
  - IL2RA

Th1 cell function
- IL12B* 
  - SOCS1* 
  - STAT1/STAT4 
  - IL18RAP, IL1R1 
  - IFNG 
  - IL27 
  - LGALS9

Th17 and B cell function
- IL2/IL21 
  - DOK3 
  - RASGRP1 
  - REL 
  - CXCR5 
  - GPR183 
  - PRKCB

Efficacy of treatment
- e.g., response to anti-TNF therapy: IL23R²

Side effects of therapy
- e.g., risk of mycobacterial infection: IL12B³, TYK2³, STAT3³

Bacterial, fungal and viral recognition
- NOD2* 
- RIPK2 
- LGALS9 
- CARD9* 
- FUT2 
- IFNGR2, IFNAR1 
- SP140 
- LACC1 
- IFIH1 
- CXCR5

Autophagy, APC function, ER stress response
- ATG16L1* 
- IRGM 
- LRRK2, SMURF1 
- MST1* 
- CD40 
- TNFRSF9, TRAF3IP2 
- CCL13, CCL2 
- PTGER4* 
- IRF8 
- FCGR2A 
- ORMDL3 
- ERAP2/ERAP1

Genotyping

Diagnosis of Crohn’s disease

INNATE IMMUNITY

Predicting treatment response
Microbial Diversity in Crohn’s Disease

- **Phyla**
  - Firmicutes
  - Bacteroidetes
  - Proteobacteria
  - Actinobacteria

- **Main groups of bacteria**
  - **Firmicutes**
    - *Fusobacterium* subgroup
    - *Porphyromonas* subgroup
    - *Prevotella* subgroup
    - *Bacteroides* subgroup
    - *Clostridium* subgroup
    - *Bifidobacterium* subgroup
    - *Atopobium* group
    - *Enterococcus* group
    - *Sporomusa* group
    - *Eubacterium clyndroides*
    - *Clostridium aurantibutyricum* group
    - *Clostridium amonobutyricum* group
    - *Clostridium coccoides* group
    - *Clostridium leptum* subgroup
  - **Bacteroidetes**
    - *Bacteroides distasonis* subgroup
    - *Prevotella* subgroup
    - *Bacteroides fragilis* subgroup
  - **Proteobacteria**
    - *Unclassified*
  - **Actinobacteria**
    - *Unclassified*

- **Number of OTUs** (operational taxonomic units)

- Healthy participants vs. Patients with Crohn’s disease

Existing Treatment Paradigms
Management of Mild to Moderate UC

**Oral 5-ASAs**
- Mesalamine 1.5–4.8 g/d
- Balsalazide 6.75 g/d
- Sulfasalazine 4–6 g/d

**Distal** (left-sided, proctitis)

**Induction**

**1st-Line**
- Rectal 5-ASA or Rectal steroid
- Oral steroid
- IV Steroid
- Infliximab, Adalimumab

**2nd-Line**

**3rd-Line**

**Maint**

5-ASA, AZA/6-MP, IFX/ADA

Importance of Adherence: Sustained Remission of IBD

Why Is My UC Patient Refractory?

• Is 5-ASA hypersensitivity colitis a possibility?
  • Sulfasalazine and 5-ASA can cause a paradoxical worsening of colitis
  • Can mimic “steroid-dependency”
  • Consider trial of 5-ASA cessation

• Is the patient on NSAIDs?
  • Consider trial of NSAID cessation
  • Consider switch to celecoxib

Clostridium difficile and Refractory UC: Milwaukee

Increasing percentage of C. diff infections are IBD patients

Immediate and Prolonged Outcomes of Corticosteroid Therapy in UC—Olmsted County, MN (1970-93)

30-Day Responses (n = 63)
- Complete: 54% (n = 34)
- Partial: 30% (n = 19)
- None: 16% (n = 10)

1-Year Responses (n = 63)
- Steroid-dependent: 22% (n = 14)
- Prolonged Response: 49% (n = 31)
- Surgery: 29% (n = 18)

Estimate of Efficacy of AZA for Treatment Success in UC Patients: Meta-Analysis

Pooled RR Estimate Across Five Trials

Infliximab for UC: ACT 1 and ACT 2
Clinical Remission

ACT 1

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo</th>
<th>IFX 5 mg/kg</th>
<th>IFX 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 Weeks</td>
<td>15</td>
<td>39</td>
<td>32</td>
</tr>
<tr>
<td>30 Weeks</td>
<td>16</td>
<td>34</td>
<td>37</td>
</tr>
<tr>
<td>54 Weeks</td>
<td>17</td>
<td>35</td>
<td>34</td>
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</table>

act 2

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo</th>
<th>IFX 5 mg/kg</th>
<th>IFX 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 Weeks</td>
<td>6</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
<td>30 Weeks</td>
<td>11</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

† P ≤ 0.002 vs placebo
‡ P ≤ 0.003 vs placebo
§ P = 0.001 vs placebo

ACT1/2 Trials: Survival Free of Colectomy

UC Success: AZA vs. IFX vs. AZA+IFX for Moderate to Severe UC

Conclusion: IFX+AZA superior to both AZA and IFX monotherapy in inducing steroid-free remission

Cyclosporine vs. Infliximab for Acute Severe UC

- 110 patients steroid refractory UC
- Treatment failure
  - No response day 7
  - No steroid-free remission day 98
  - Relapse between days 7 and 98
  - Colectomy
  - Death
- Conclusion: CyA was not superior to IFX in acute severe UC

Adalimumab for Moderate to Severe UC: Induction/Maintenance Trial (n=494)

Week 8 Endpoints

- Clinical remission: 9.3% (Placebo), 16.5% (ADA)
- Clinical response: 34.6% (Placebo), 50.4% (ADA)
- Mucosal healing: 31.7% (Placebo), 41.1% (ADA)

Week 52 Endpoints

- Clinical remission: 8.5% (Placebo), 17.3% (ADA)
- Clinical response: 18.3% (Placebo), 30.2% (ADA)
- Mucosal healing: 15.4% (Placebo), 25.0% (ADA)

Golimumab (GLM) for Moderate to Severe Ulcerative Colitis, PURSUIT Studies

**Induction of Clinical Response**

- Placebo: 29.7%
- 200/100 mg: 51.8%
- 400/200 mg: 55%

**Maintenance of Clinical Response Among Responders**

- Placebo: 31.4%
- GLM 50 mg: 47.1%
- GLM 100 mg: 50.6%

* P < 0.01 vs placebo

Management of Crohn’s Disease

Induction

Prednisone, Budesonide

AZA/6MP/MTX

Anti-TNF (Infliximab, Adalimumab, Certolizumab pegol)

Natalizumab

Maint

AZA/MTX, Anti-TNF, Natalizumab

5-Aminosalicylate (5-ASA, Mesalamine) for Crohn’s Disease

• Widely used for induction and maintenance of response and remission in mild to moderate Crohn’s disease
• Meta-analyses showed no efficacy for induction or maintenance of remission
• Fortunately, use in clinical practice gradually declining
Immediate and Prolonged Outcomes of Corticosteroid Therapy in Crohn’s Disease—Olmsted County, MN (1970-93)

30-Day Responses (n=74)
- Complete 58% (n=43)
- Partial 26% (n=19)
- None 16% (n=12)

1-Year Responses (n=74)*
- Steroid dependent 32% (n=24)
- Prolonged response 28% (n=21)
- Surgery 38% (n=28)

*One patient lost to follow-up

ORAL BUDERSONIDE IN ACTIVE CROHN'S DISEASE

CD - Therapy of Active Disease

% Patients in remission

- Budesonide (9mg/d)
- Mesalazine (4g/d)
- Prednisolone (40mg/d)

NEJM 1994; 331:836
NEJM 1998; 339:370
NEJM 1994; 331:842
Updated Meta-Analysis of AZA/6-MP for Crohn’s Disease: Benefit Is Not So Clear

Induction of Remission

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 Azathioprine/6-MP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candy (1995)</td>
<td>9</td>
<td>11</td>
<td>2.2%</td>
<td>0.74 (0.36, 1.54)</td>
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<tr>
<td>Ewe (1993)</td>
<td>5</td>
<td>13</td>
<td>1.7%</td>
<td>0.38 (0.17, 0.89)</td>
</tr>
<tr>
<td>Oren (1997)</td>
<td>23</td>
<td>26</td>
<td>12.8%</td>
<td>0.93 (0.69, 1.26)</td>
</tr>
<tr>
<td>Reinisch (2008)</td>
<td>27</td>
<td>29</td>
<td>5.5%</td>
<td>1.08 (0.88, 1.20)</td>
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<tr>
<td>Summers (1979)</td>
<td>38</td>
<td>57</td>
<td>21.8%</td>
<td>0.87 (0.69, 1.10)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>197</td>
<td>183</td>
<td>44.0%</td>
<td>0.87 (0.71, 1.06)</td>
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<tr>
<td>Total events</td>
<td>102</td>
<td>115</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2$ = 5.05, df = 4 (P = 0.28); $I^2 = 21%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 1.36 (P = 0.17)</td>
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</table>

Prevention of Relapse

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 Azathioprine</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candy (1995)</td>
<td>10</td>
<td>17</td>
<td>21.9%</td>
<td>0.47 (0.28, 0.77)</td>
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<tr>
<td>Summers (1979)</td>
<td>17</td>
<td>36</td>
<td>22.9%</td>
<td>0.89 (0.55, 1.42)</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>27</td>
<td>78</td>
<td>44.8%</td>
<td>0.64 (0.34, 1.23)</td>
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<tr>
<td>Total events</td>
<td>27</td>
<td>53</td>
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<tr>
<td>Heterogeneity: $\chi^2$ = 3.53, df = 1 (P = 0.06); $I^2 = 72%$</td>
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<tr>
<td>Test for overall effect: Z = 1.34 (P = 0.18)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Khan KJ et al, Am J Gastroenterol 2011;106:630-42.
Methotrexate for Crohn’s Disease

- Methotrexate 25 mg/week IM/SC (and possibly 15 mg/week orally) is effective for inducing remission in patients with steroid-dependent and steroid-refractory active CD
- Methotrexate 15-25 mg/week IM/SC is effective for maintenance of remission and steroid sparing in CD
- Less “lymphomagenic” than thiopurines?
## Construct of Biologic Agents Used in Crohn’s Disease

<table>
<thead>
<tr>
<th>Category</th>
<th>Agent</th>
<th>Type</th>
<th>Humanization</th>
<th>Recombinant</th>
<th>Fusion Protein</th>
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<tbody>
<tr>
<td>Murine</td>
<td>Infliximab</td>
<td>Chimeric</td>
<td>IgG(_1) isotype</td>
<td>75% human</td>
<td></td>
</tr>
<tr>
<td>Chimeric</td>
<td>CDP571</td>
<td>Humanized</td>
<td>IgG(_4) isotype</td>
<td>95% human</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Natalizumab</td>
<td></td>
<td></td>
<td>100% human</td>
<td></td>
</tr>
<tr>
<td>Humanized</td>
<td>Etanercept (p75)</td>
<td>Human</td>
<td>IgG(_4) isotype</td>
<td>95% human</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Onercept (p55)</td>
<td>Recombinant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pegylated</td>
<td>CDP870</td>
<td>Humanized</td>
<td>IgG(_4) isotype</td>
<td>95% human</td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>Certolizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adalimumab</td>
<td>D2E7</td>
<td>IgG(_1) isotype</td>
<td>100% human</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Golimumab</td>
<td></td>
<td></td>
<td></td>
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</table>
Induction of Clinical Remission at Week 4 In Crohn’s Disease: Certolizumab, Adalimumab, Infliximab


* p<0.05
NS Non-significance
Net Remission at Six Months: Certolizumab, Adalimumab, Infliximab

Certolizumab Pegol – PRECISE 2

- Open-label Induction Week 6
  - Pbo: 64.1%
  - CzP: 47.9%
- Week 26 remission
  - Pbo: 28.6%
  - CzP: 18.3%
- Net remission week 26
  - Pbo: 30.7%
  - CzP: 18.3%

Infliximab – ACCENT I

- Open-label Induction Week 2
  - Pbo: 58.5%
  - IFX: 21.0%
- Week 30 remission
  - Pbo: 39.0%
  - IFX: 12.3%
- Net remission week 30
  - Pbo: 22.8%
  - IFX: 12.3%

Certolizumab Pegol – PRECISE 1

- Open-label Induction Week 4
  - Pbo: 18.3%
  - CzP: 29.5%
- Week 26 remission
  - Pbo: 18.3%
  - CzP: 29.5%
- Net remission week 26
  - Pbo: 18.3%
  - CzP: 29.5%

Adalimumab - CHARM

- Open Label Induction Week 4
  - Pbo: 58.0%
  - ADA: 40.0%
- Week 26 remission
  - Pbo: 17.0%
  - ADA: 9.9%
- Net remission week 26
  - Pbo: 23.2%
  - ADA: 9.9%

References:
Mucosal Healing With Adalimumab in CD (EXTEND)

Primary End Point

Week 12 ITT: 13.1% (8/61) vs. 27.4% (17/62) for ADA induction (160/80 mg)/placebo vs. ADA QOW (40 mg) respectively, $P=0.056$, NS.

Week 52 ITT: 0% (0/61) vs. 24.2% (15/62) for ADA induction (160/80 mg)/placebo vs. ADA QOW (40 mg) respectively, $P<0.001$.

ITT, intent-to-treat; NS, not significant

Natalizumab (Anti-Alpha 4 Integrin) Therapy for Crohn’s Disease

- Monoclonal antibody to alpha 4 integrin
- Target molecules are VCAM-1 and MAdCAM-1
- Blocks lymphocyte trafficking from vascular space to tissues
- Effective for induction and maintenance of response and remission and steroid-sparing

Villablanca EJ et al, Gastroenterology 2011;140:1776-84.
ENACT-2 Natalizumab in Active Crohn’s Disease: Maintenance of Clinical Response (70 points) in Week 12 Responders

**Percent Response**

- At Week 36: Placebo 37, Natalizumab 67
- At Week 60: Placebo 24, Natalizumab 59

**Percent Remission**

- At Week 36: Placebo 30, Natalizumab 55
- At Week 60: Placebo 22, Natalizumab 55

*P ≤ 0.001

Natalizumab-Related Progressive Multifocal Leukoencephalopathy

- Reactivation of the human JC polyoma virus
- Severe neurologic disability or death
- Has occurred in 398 patients out of approximately 125,000 treated as of September 2013
  - All but two cases occurred in MS patients (less than 2% of natalizumab use in US is for Crohn’s)
- FDA mandated risk management program (TOUCH)
- Risk stratified by JC virus serology (99% of PML with available pre-PML sera are anti-JCV-positive)
- Use restricted to patients who have failed anti-TNF therapy
- Must be administered as monotherapy (without other immunosuppressive agents)
Evolving Treatment Paradigm

Using Available Data for Risk Prognostication
## Baseline Factors Associated with Time to Surgery: Crohn’s, Olmsted County, 1970-2004

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.6</td>
<td>1.02 - 2.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Small bowel</td>
<td>3.4</td>
<td>1.9 - 6.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ileocolonic</td>
<td>3.3</td>
<td>1.8 - 5.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Upper gut</td>
<td>4.0</td>
<td>1.2 – 13.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.7</td>
<td>1.1 – 2.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Penetrating</td>
<td>2.7</td>
<td>1.1 – 6.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Stricturing</td>
<td>1.4</td>
<td>0.2 – 10.4</td>
<td>0.74</td>
</tr>
<tr>
<td>Early steroids</td>
<td>1.6</td>
<td>1.03 – 2.5</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Peyrin-Biroulet L et al, Gastroenterology Suppl 2010 (DDW)
## Risk Factors Associated With Intestinal Complications: Crohn’s, Olmsted County

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal ileum</td>
<td>7.8</td>
<td>3.5 – 17.4</td>
</tr>
<tr>
<td>Ileocolonic</td>
<td>5.6</td>
<td>2.3 – 13.9</td>
</tr>
<tr>
<td>Upper GI</td>
<td>9.5</td>
<td>3.0 – 30.1</td>
</tr>
<tr>
<td>Perianal fistula</td>
<td>1.7</td>
<td>0.99 – 2.86</td>
</tr>
</tbody>
</table>

Advances in IBD Natural History: Predictors of More Severe Disease

- Crohn’s disease
  - Young age of onset (<40 years)
  - Ileal or ileocolonic extent
  - Fistulizing disease at diagnosis
  - Early need for steroids

- Ulcerative Colitis
  - Extensive colitis
  - Male gender
  - Early need for steroids
  - Early hospitalization

Evolving Treatment ParadIGms

Treat Earlier in the Course of Crohn’s Disease
Top-Down vs Step-Up: Early Infliximab or Standard Therapy

Clinical remission (CDAI <150), off corticosteroids, and no intestinal resection

- Wk 14: Step-Up 42%, Top-Down 47% (P≤0.001)
- Wk 26: Step-Up 36%, Top-Down 45% (P=0.006)
- Wk 52: Step-Up 33%, Top-Down 60% (P=0.028)
- Wk 78: Step-Up 57%, Top-Down 62% (P=0.797)
- Wk 104: Step-Up 65%, Top-Down 60% (P=0.431)

N=133

SONIC: Corticosteroid-Free Clinical Remission at Week 26

Primary Endpoint

Proportion of Patients (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA + placebo</td>
<td>30.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IFX + placebo</td>
<td>44.4</td>
<td>0.009</td>
</tr>
<tr>
<td>IFX + AZA</td>
<td>56.8</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Infliximab Effect on Hospitalizations and Surgeries – ACCENT I

Evolving Treatment Paradigms

Treatment Decisions Based on Objective Evidence
CDAI Versus CDEIS During Treatment With Prednisolone

- Complete lack of correlation between CDAI (primarily symptom-based) and endoscopic inflammation
- Symptoms and signs of Crohn’s are neither sensitive nor specific

Modigliani R et al, Gastroenterology 1990
Is It Really “Loss of Response” or “Non-Response”? Are Symptoms Due to IBD?

- Celiac disease
- Bacterial overgrowth
- Bile salt diarrhea
- Irritable bowel syndrome
- Hypersensitivity colitis
- Short bowel syndrome
- Carbohydrate malabsorption (lactose and fructose)
Bacterial Overgrowth in Crohn’s Disease (n=153)

• Hydrogen glucose breath test in symptomatic patients
  – Increased stool frequency, increased flatulence or pain
• 25% had positive breath tests
• Risk factors
  – Multiple resections
  – Partial colonic resection
  – Ileocolonic disease

SONIC: Corticosteroid-Free Clinical Remission at Week 26 by Baseline Endoscopy Status

Colombel JF et al, N Engl J Med 2010
Paradigm Shift for Making Treatment Decisions in Patients with Inflammatory Bowel Disease

• OLD: Treat based on symptoms
  – But: symptoms are insensitive and non-specific for bowel inflammation

• NEW: Treat based on objective markers of inflammation
  – Serologic (CRP reduction)
  – Endoscopic (mucosal healing)
  – Radiographic (CTE/MRE improvement)
  – Goal should be “mucosal healing” or absence/reduction in inflammation
  – This will be the only way we can hope to alter the natural history of Crohn’s disease
Evolving Treatment Paradigms

Treatment Endpoint Based on Objective Evidence Not Symptoms
Steroid Avoidance Had More Endoscopic Healing at 2 Years
Secondary End Point of the Top-Down/Step-Up Trial

\[ P = 0.0028 \]

...and these patients did better in the next 2 yrs!

Patients In Remission (%)

<table>
<thead>
<tr>
<th>Remission Off Steroids</th>
<th>Off Steroids, No Anti-TNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>70.8</td>
<td>62.5</td>
</tr>
<tr>
<td>27.3</td>
<td>18.2</td>
</tr>
</tbody>
</table>

CT Enterography Healing: Equivalent to Mucosal Healing at Endoscopy?

Resolution of intramural inflammation on maintenance infliximab

MRI and Crohn’s Activity: MaRIA

- Index based on wall thickness, relative contrast enhancement, MRI edema, and MRI ulcers
- 48 patients (29 active; 19 inactive disease)
- Receiver operator characteristic (ROC) curve for derivation (0.97) and validation (0.96) compared to ileocolonoscopy (CDEIS)
- More accurate for severe disease as opposed to active disease

MaRIA, magnetic resonance index of activity

Implementing “Treat to Target” in IBD: Mucosal Healing as the Target

• Primary target: absence of mucosal ulceration
• Level of target may be influenced by comorbidities and drug-related risks
• Desired target should be maintained indefinitely
• Use both symptoms and objective measures of inflammation (endoscopic or radiologic) to guide treatment decisions
• Assess mucosal healing every 6 months till target is achieved, then every 1-2 years after, adjust according to degree of inflammation

A Proposed Algorithm for Disease Monitoring in IBD

Baseline assessment of disease activity by endoscopy paired with surrogate marker

Choice of initial therapy based on severity and prognosis of patient

3-6 months

Re-assessment of disease activity directly or with surrogate marker

Healing Documented?

No

Discussion with patient treatment options

Is patient willing to proceed with your recommendations

No

Clinical follow-up

Yes

Adjust therapy

If no other treatment options left

Clinical follow-up that includes assessment of disease stability

6-12 months

3-6 months

Discussion with patient treatment options

No

Clinical follow-up

Yes

Adjust therapy

Slide compliments of David T. Rubin, MD
Challenges to Mucosal Healing in Crohn’s Disease

- It can’t be achieved in many/most patients
- Unclear how much healing is really needed to affect outcomes
- It is unknown what incremental healing can be achieved by dose escalation or switching therapies
- We don’t know the appropriate time interval between changes in therapy and subsequent reassessment
- Can surrogates of endoscopic healing be used?

Evolving Treatment Paradigm

Therapeutic Drug Monitoring
Metabolism of AZA/6-MP 101

AZA → 6-MP

XO

HPRT

6-thiouric acid

6-MMP

6-TGNs

TPMT
TPMT Activity in 407 New Zealand Patients

## Meta-Analysis: Association Between 6-TGN Levels and Clinical Remission

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Patients (Remission)</th>
<th>6TGN Threshold</th>
<th>Fraction Above Threshold Remission</th>
<th>Fraction Below Threshold Remission</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dubinsky 2000</td>
<td>92 (30)</td>
<td>235</td>
<td>.78</td>
<td>.40</td>
<td>5.07</td>
<td>2.62-9.83</td>
</tr>
<tr>
<td>Gupta 2001</td>
<td>101 (47)</td>
<td>235</td>
<td>.56</td>
<td>.43</td>
<td>1.65</td>
<td>0.73-3.75</td>
</tr>
<tr>
<td>Belaiche 2001</td>
<td>28 (19)</td>
<td>230</td>
<td>.75</td>
<td>.65</td>
<td>1.62</td>
<td>0.26-10.2</td>
</tr>
<tr>
<td>Cuffari 2001</td>
<td>82 (47)</td>
<td>250</td>
<td>.86</td>
<td>.35</td>
<td>11.63</td>
<td>3.78-35.7</td>
</tr>
<tr>
<td>Goldenberg 2004</td>
<td>74 (15)</td>
<td>235</td>
<td>.24</td>
<td>.18</td>
<td>1.47</td>
<td>0.47-6.42</td>
</tr>
<tr>
<td>Achkar 2004</td>
<td>60 (24)</td>
<td>235</td>
<td>.51</td>
<td>.22</td>
<td>3.80</td>
<td>1.17-12.4</td>
</tr>
<tr>
<td><strong>Pooled Estimate</strong></td>
<td></td>
<td></td>
<td>0.62 (0.43-0.80)</td>
<td>0.36 (0.25-0.48)</td>
<td>3.27</td>
<td>1.71-6.27</td>
</tr>
</tbody>
</table>

Osterman MT et al. Gastroenterology 2006:130(4);1047-1053
Effect of Trough Serum Infliximab Concentrations on Clinical Outcome at >52 Weeks

ADA Trough Above 0.33 µg/mL Predicts Clinical Response

Log Rank: $P=0.01$

- ADA TR>0.33 µg/mL, n=104
- ADA TR<0.33 µg/mL, n=16

What Factors Influence the Pharmacokinetics of TNF Antagonists?

Decreases drug clearance

- Concomitant immunosuppressives

Increases drug clearance

- Anti-drug antibodies
- Low serum albumin
- High baseline CRP
- High baseline TNF concentration
- High body mass index
- Male sex

CRP=C-reactive protein

Treatment Algorithm in IBD Patients With Clinical Symptoms (Infliximab and HACA Concentrations)

- **Positive HACA**
  - Change to another anti-TNF agent
  - Persistent disease
  - Change to non-anti-TNF agent

- **Therapeutic IFX concentration**
  - Active disease on endoscopy/radiology?
    - yes
      - Change to different anti-TNF agent
    - no
      - Investigate alternate etiologies

- **Subtherapeutic IFX concentration**
  - Increase infliximab dose or frequency
  - Change to different anti-TNF agent
  - Change to different anti-TNF agent
  - Change to non-anti-TNF agent

Active Monitoring of Anti-TNF Levels May Ensure Durability of Response

Prospectively optimized IFX trough concentrations to a target range of 5-10 μg/mL

Probability on Infliximab

Optimized
Not Optimized

Weeks

Effect of Concomitant Azathioprine or Methotrexate on Anti-drug Antibodies

Patient 1
Start MTX

Patient 3
Start AZA

IFX levels closed squares
ATI open squares

Weeks
Concentration (mcg/mL)

0 10 20 30 40 50

0 5 10 15 20 25

New Therapies
Vedolizumab for Moderate to Severe UC Induction, GEMINI I

- Monoclonal antibody to alpha-4 beta-7 integrin
- Blocks lymphocyte homing in the gut
- Much more gut-specific than natalizumab—shouldn’t cause PML
- Over 3000 patients treated to date—no PML

Vedolizumab for Maintenance of Remission in UC-Week 52, GEMINI I

Vedolizumab in Moderate to Severe Crohn’s Disease-GEMINI II

Ustekinumab for Moderate to Severe Crohn’s Disease: Phase 2b, CERTIFI

- Monoclonal antibody to p40 subunit of interleukins-12 and -23
- Commercially approved for psoriasis
- Secondary endpoints of clinical response at weeks 16, 20 and 22 were met
- Phase 3 trials underway

* P < 0.05 versus placebo

UNITI-2 Trial
Ustekinumab in Anti-TNF-Naïve CD Patients

Clinical Response at Week 6
(≥100 point CDAI reduction)

- Placebo: 28.7%, n=209
- 130 mg: 51.7%, n=209
- ~6 mg/kg*: 55.5%, n=209
- Combined: 53.6%, n=418

*Weight-range based UST doses approximating 6 mg/kg: 260 mg (weight ≤55 kg), 390 mg (weight >55 mg and ≤85 kg), 520 mg (weight >85 kg).

Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes prior to designated analysis time point are considered not to be in clinical response, regardless of their CDAI score.

Subjects who had insufficient data to calculate the CDAI score at designated analysis endpoint are considered not to be in clinical response.

UNITI-1 Trial
Ustekinumab in CD Patients Failing Anti-TNF Therapy

Clinical Response at Week 6
(≥100 point CDAI reduction)

*Weight-range based UST doses approximating 6 mg/kg: 260 mg (weight ≤55 kg), 390 mg (weight >55 mg and ≤85 kg), 520 mg (weight >85 kg).
Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes prior to designated analysis time point are considered not to be in clinical response, regardless of their CDAI score. Subjects who had insufficient data to calculate the CDAI score at designated analysis endpoint are considered not to be in clinical response.

Mongersen (GED-0301): Phase 2 Trial in Steroid-dependent or -resistant CD

Clinical Remission at Week 12

Tofacitinib for Moderately to Severely Active UC - Phase 2

- Janus kinase (JAK) antagonist
- Blocks downstream signaling of many pro-inflammatory interleukins
- Small molecule (oral)
- Recently approved for rheumatoid arthritis (Xeljanz)
- Increases LDL, HDL cholesterol

Week 8

Clinical Response

- Placebo
- 0.5mg BID
- 3mg BID
- 10mg BID
- 15mg BID

Clinical Remission

Selected Pipeline Drugs for IBD

Crohn’s

• AMG181 - anti-α4β7 integrin adhesion molecule
• Ustekinumab (Stelara) - anti-IL-12/23
• PF00547659—Anti-MAdCAM-1 (adhesion molecule blocker)
• Etrolizumab-anti-β7 integrin
• Mongerson-oral SMAD7 antisense oligonucleotide

Ulcerative Colitis

• AMG181
• Tofacitinib-small molecule Janus kinase antagonist
• Etrolizumab
Conclusions

• Crohn’s disease and ulcerative colitis are chronic inflammatory conditions which can result in high morbidity

• 5-ASA products remain the mainstay of treatment of UC

• Prednisone is effective for inducing clinical response in the short term but is not effective maintenance for either UC or Crohn’s

• AZA, 6-MP and MTX are steroid-sparing agents
Conclusions

• Anti-TNF agents are effective for inducing and maintaining response/remission in Crohn’s and UC

• Anti-TNF agents can reduce need for hospitalizations and surgeries in Crohn’s and UC

• Natalizumab is an option for Crohn’s disease patients who are anti-TNF refractory, but carries a risk of PML
Conclusions

• Use objective markers of inflammation rather than symptoms to make treatment decisions

• Follow up on changes in therapy with objective markers of inflammation

• Use drug monitoring when available